Conflict of Interest and Clinical Re$earch:

The Ethical and Regulatory Aspects of Clinical Research

October 11, 2006

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Yale University School of Medicine

Disclosure

- Research Support: Boehringer-Ingelheim

Disclosure

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Use Plavix

Disclosure

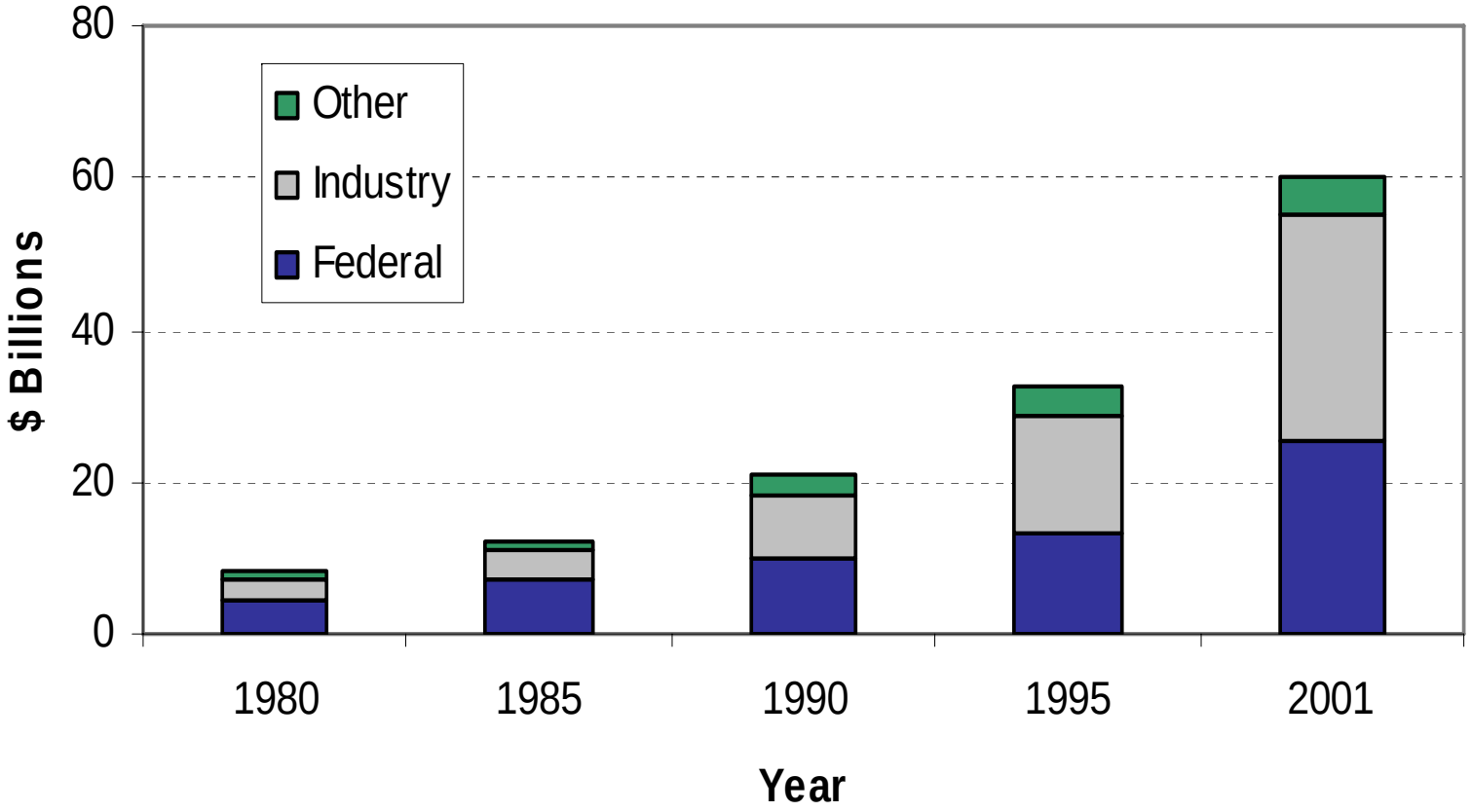
- Research Support: Boehringer-Ingelheim

Conflict of Interest and Clinical Research Objectives

- Evolution of the medical research landscape
- How financial conflicts bias science, scientists, and institutions
- Repairing the system

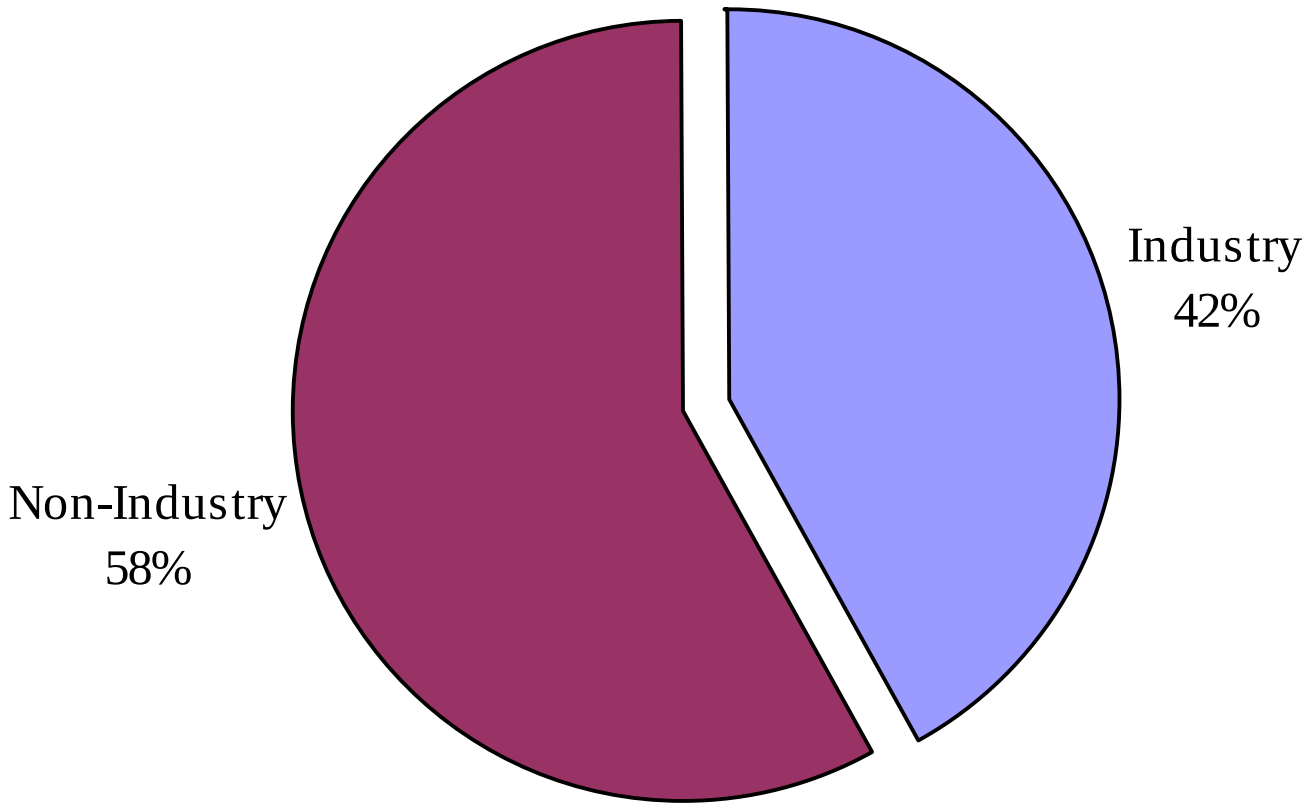
I - Evolution of the Research Landscape

National Biomedical Research Expenditures



Source: PhRMA Industry Profile 2004; NIH Office of the Director; NSF,2000

Sponsorship of published RCTs



Gross et al. *BMJ*, 2002.

Prevalence of financial conflicts

- 22% of community internists participated in industry trials in 2003
- 28% of faculty received industry research funds (1996)
- 124 academic institutions held equity in businesses engaged in research at the same institution

Ashar et al. *JGIM*, 2004.

Blumenthal et al. *N Eng J Med*. 1996

Financial Conflict of Interest

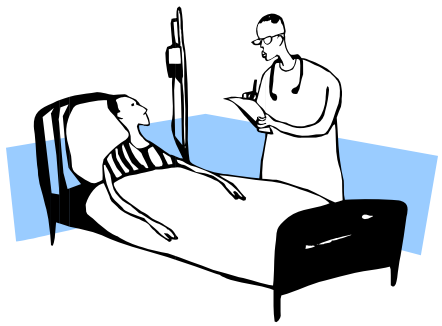
"Situations in which financial considerations may compromise, or have the appearance of compromising, an investigator's judgement in conducting or reporting research."

1990 AAMC Guidelines

Many types of conflicts

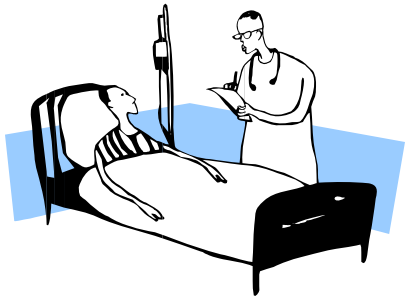
- Non-financial
  - Desire to prove prior hypotheses were correct
  - Self-promotion/peer recognition
  - Political agendas
  - Religious beliefs
- Financial
  - Study support
  - Investigator support to conduct a study
  - Other:
    - Royalties/patents
    - Expert Witness
    - “Insider” Information

II - How COI Can Promote Bias



Bench to Bedside

Scientific Evidence



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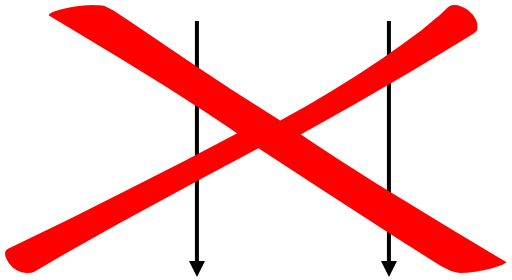
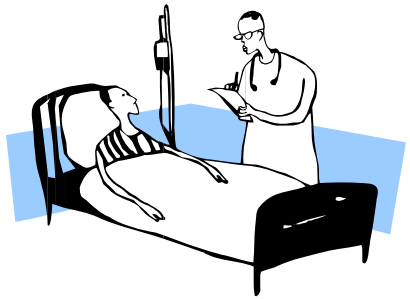
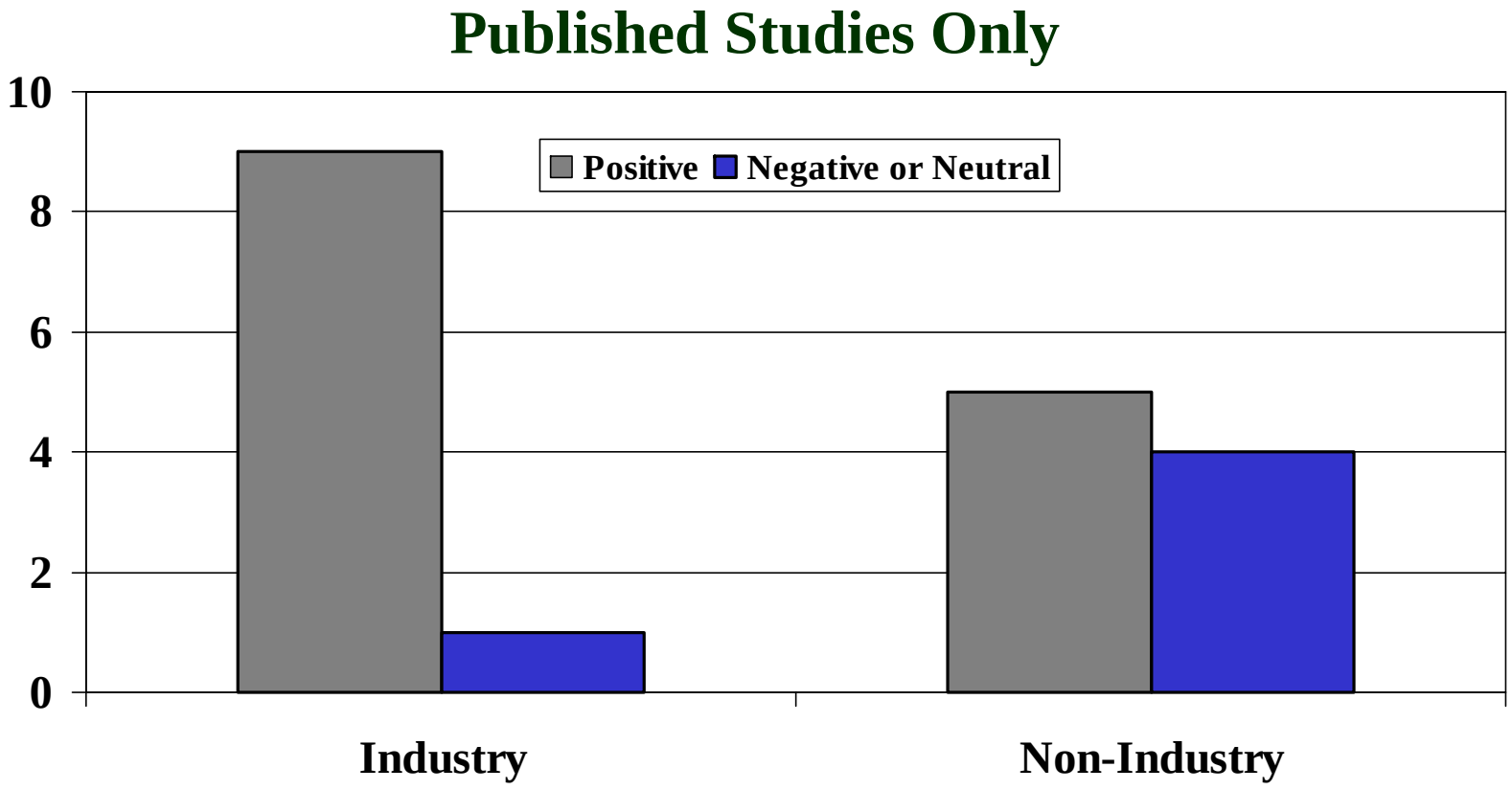


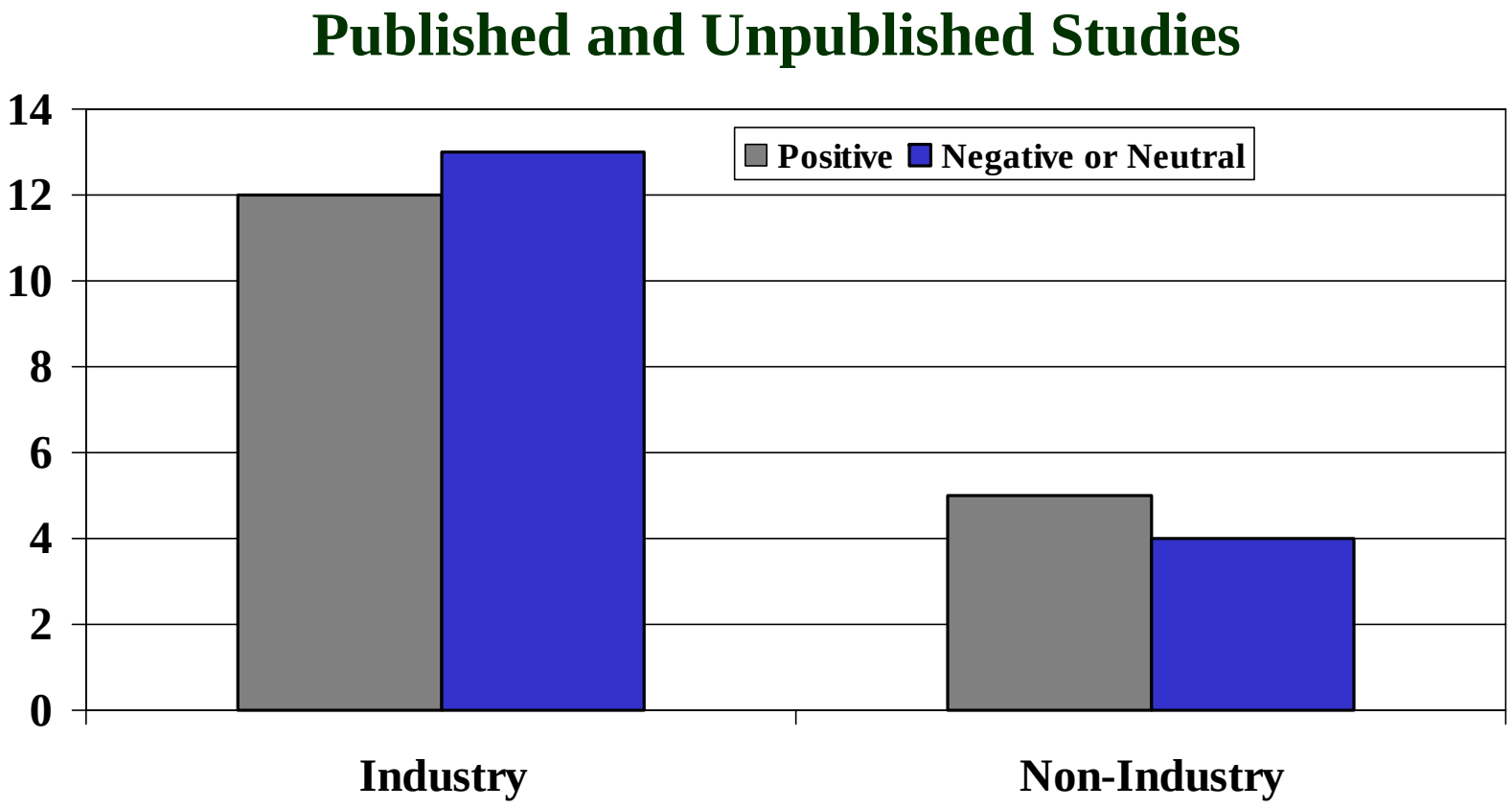


Suppressing dissemination of evidence: SSRI RCTs in Children



Source: Goozner et al, Center for Science in the Public Interest, 2004

Suppressing dissemination of evidence: SSRI vs. Placebo in Children



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Bayer and Cerivastatin

- July 1999 trial data:
  - High Dose Cerivastatin ⟶ CPK ⇈ in 12%
  - No further study of high dose cerivastatin

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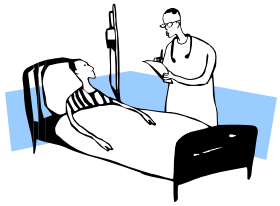
- August 1999 Bayer internal document:

  "*The large percentage of patients experiencing CK elevations led to a consensus not to publish the results of this study*"

Bench to Bedside

Data Analysis
& Interpretation

Scientific Evidence



Celecoxib

Long-term

Arthritis

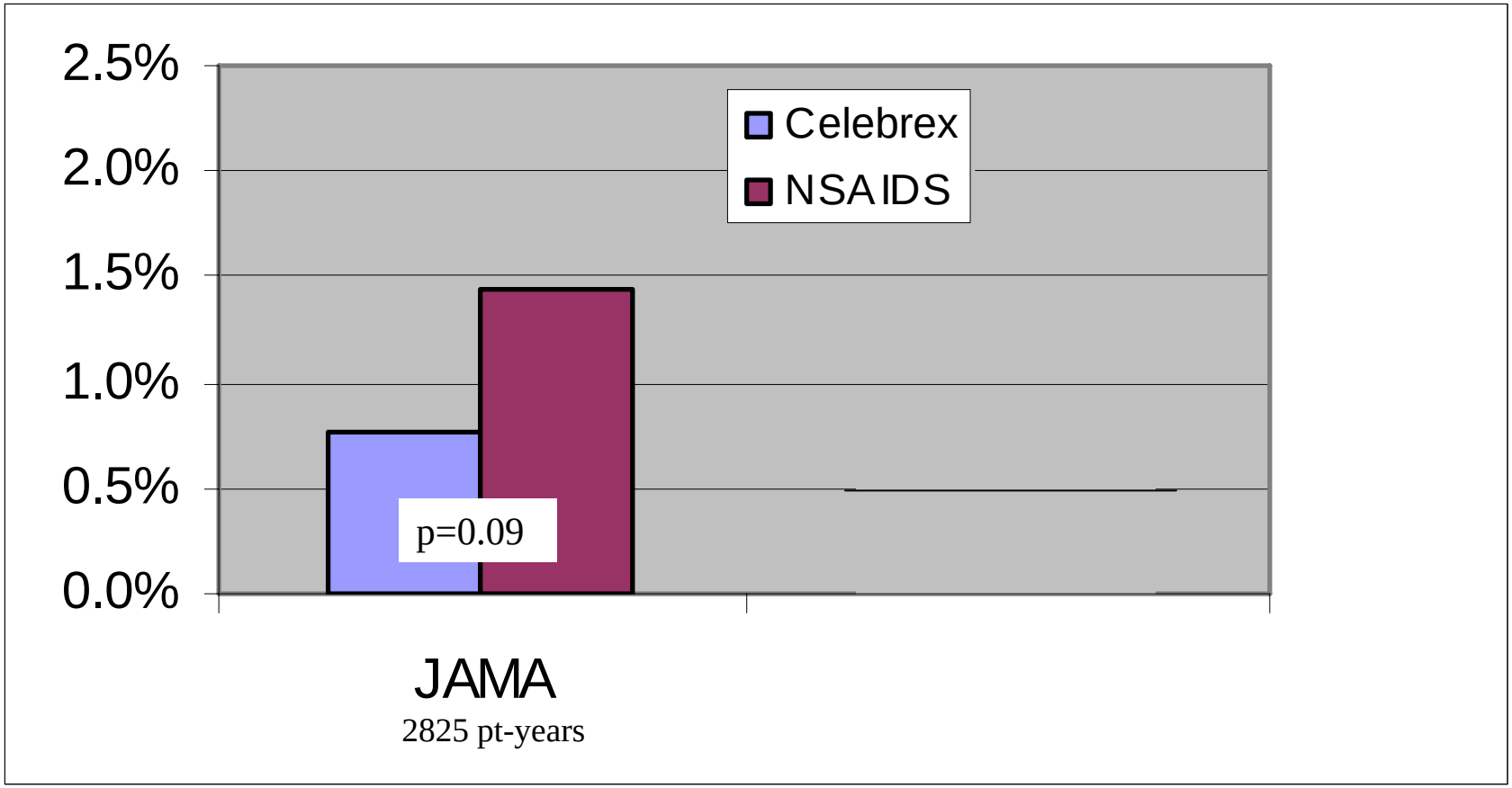
Safety

Study

CLASS Design

- RCT
- Celecoxib Vs. NSAIDS
- 1° Endpoint: Complicated Ulcer

CLASS Study: Incidence of ulcer complications at 6 months



Sources: Silverstein et al, JAMA; 2000; 284; 1247-55
FDA Arthritis Advisory Panel, February 7, 2001

Study Conclusions in JAMA

Manuscript:

"Celecoxib associated with lower incidence of symptomatic and ulcer complications combined"

Silverstein et al, JAMA; 2000; 284; 1247-55

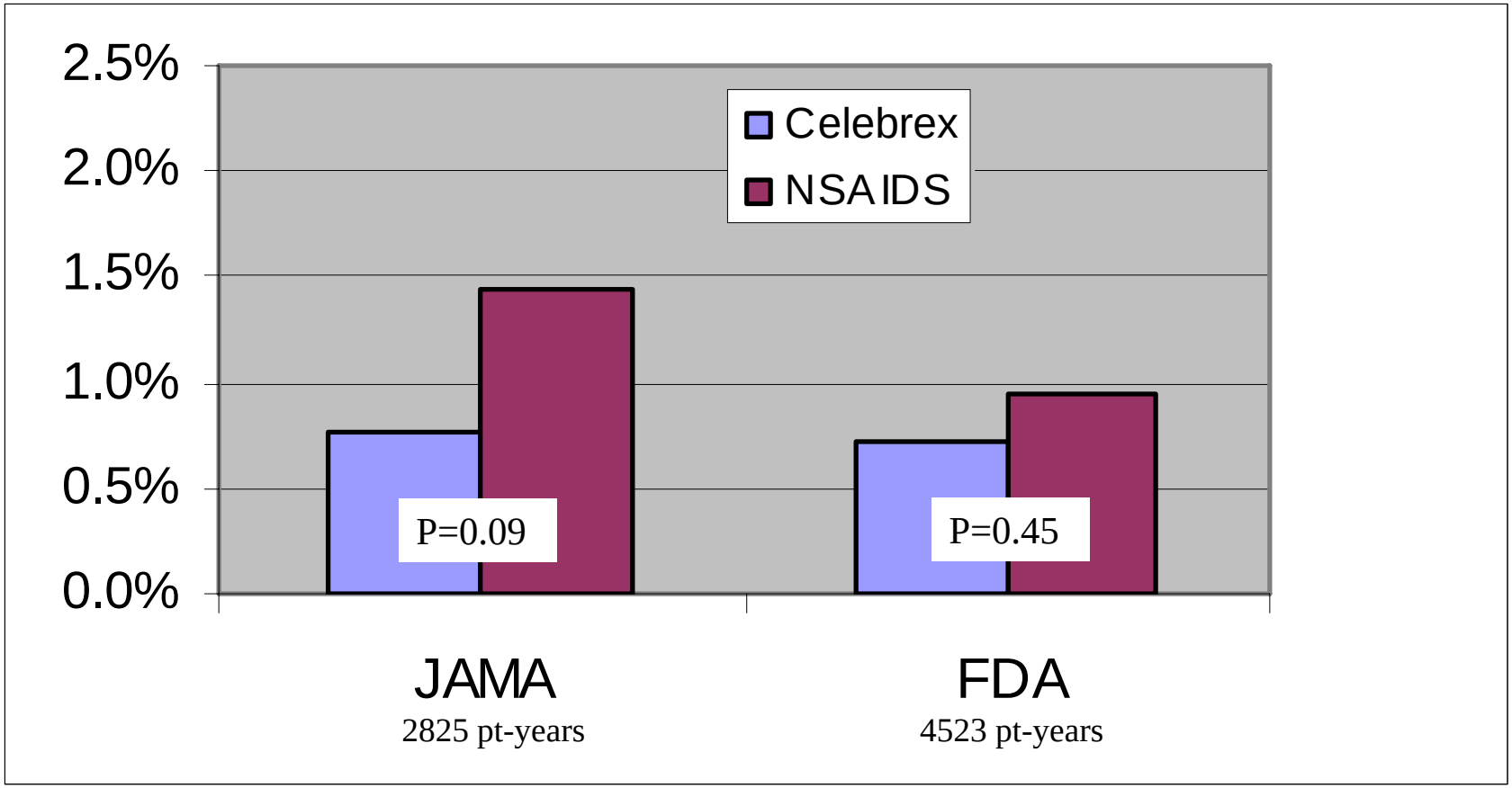
Editorial:

"….suggests that Celecoxib is effective at reducing the risk of symptomatic ulcers…..However, because this prospective analysis was limited to six months, careful future analysis will be required…."

M Wolfe, JAMA; 2000; 284; 1297-9

CLASS Study:

JAMA 6 month vs. complete 12 month follow-up



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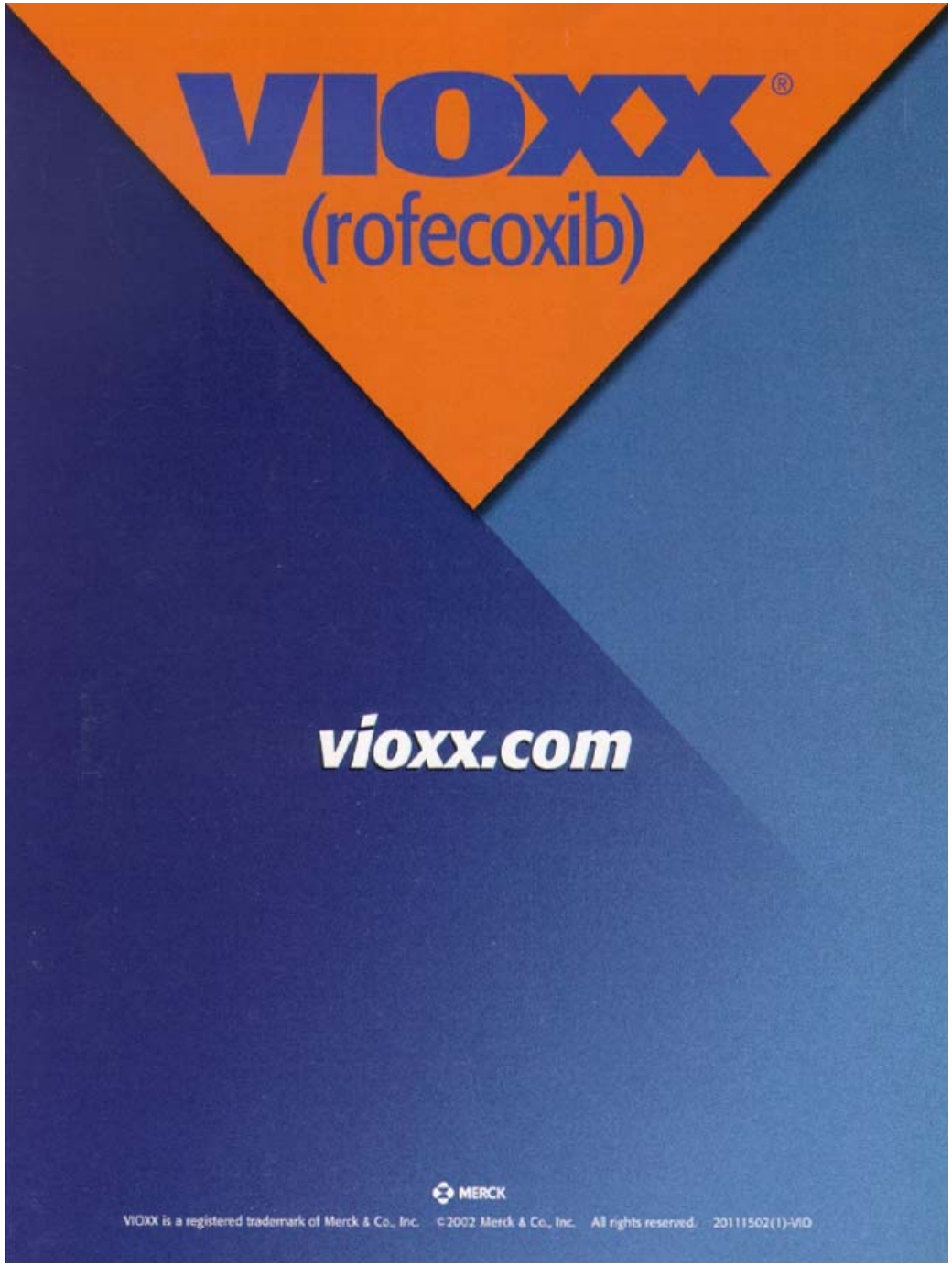
"I am furious…I wrote the editorial. I looked like a fool - but all I had available to me was the data presented in the article."

M Wolfe, Washington Post, August 2001

"We are functioning on a level of trust that was….broken."

C. DeAngelis, Washington Post, August 2001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(rofecoxib)
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COMPARISON OF UPPER GASTROINTESTINAL TOXICITY OF ROFECOXIB AND NAPROXEN IN PATIENTS WITH RHEUMATOID ARTHRITIS

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VIGOR results:

vigorously reported?

Outcome (9-months f/u)	**Rofecoxib (n=4,047)**	**Naproxen (n=4,029)**	**Relative Risk**	**P-value**
Arthritis Disability Score Δ	-0.11	-0.12	-	NS
GI Bleeds*				
Total	2.1	4.5	0.5	<0.001
Complicated	0.6	1.4	0.4	0.005
Myocardial Infarction	0.4%	0.1%	4.0	<0.05

** (per 100 pt-year)*

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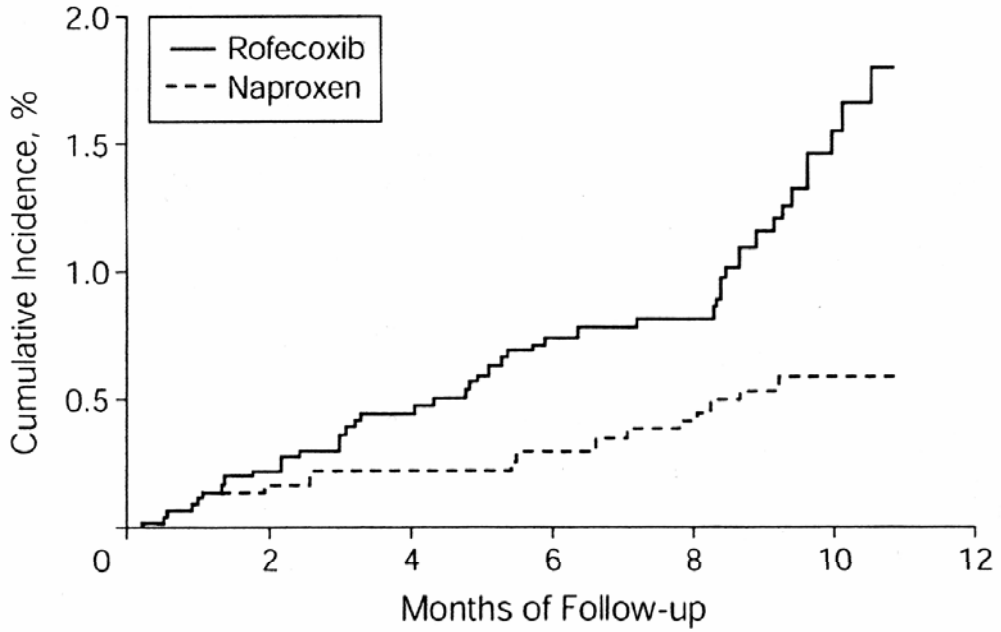
From the Institute for Work and Health, Mount Sinai Hospital, and the University Health Network, Toronto (C.B.); the Gastrointestinal Division, Department of Medicine, University of Southern California School of Medicine, Los Angeles (L.L.); Merck, Rahway, N.J. (A.R., D.S.); the Faculty of Medicine and Research Division, Universidad Nacional Autonoma de Mexico, and Hospital General de Mexico, Mexico City, Mexico (R.B.-V.); University of Texas–Houston School of Public Health, Houston (B.D.); the Department of Clinical Pharmacology, University of New South Wales and St. Vincent's Hospital, Sydney, Australia (R.D.); the Division of Rheumatology, Department of Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil (M.B.F.); the Division of Gastroenterology, School of Medical and Surgical Sciences, University Hospital, Nottingham, United Kingdom (C.J.H.); the Division of Rheumatology and Clinical Immunology, University of Maryland, Baltimore (M.C.H.); Oslo City Department of Rheumatology, and Diakonhjemmet Hospital, Oslo, Norway (T.K.K.); and the Office of Clinical Research and Training, Northwestern University School of Medicine, Chicago (T.J.S.). Address reprint requests to Dr. Bombardier at the Institute for Work and Health, 250 Bloor St. E., Suite 702, Toronto, ON M4W 1E6, Canada, or at claire.bombardier@utoronto.ca.

Arthur Weaver, M.D., Arthritis Center of Nebraska, Lincoln, was another author.

General Safety

The safety of both rofecoxib and naproxen was similar to that reported in previous studies.[20,21] The mortality rate was 0.5 percent in the rofecoxib group and 0.4 percent in the naproxen group. The rate of death from cardiovascular causes was 0.2 percent in both groups. Ischemic cerebrovascular events occurred in 0.2 percent of the patients in each group. Myocardial infarctions were less common in the naproxen group than in the rofecoxib group (0.1 percent vs. 0.4 percent; 95 percent confidence interval for the difference, 0.1 to 0.6 percent; relative risk, 0.2; 95 percent confidence interval, 0.1 to 0.7). Four percent of the study subjects met the criteria of the Food and Drug Administration (FDA) for the use of aspirin for secondary cardiovascular prophylaxis (presence of a history of myocardial infarction, angina, cerebrovascular accident, transient ischemic attack, angioplasty, or coronary bypass)[22] but were not taking low-dose aspirin therapy. These patients accounted for 38 percent of the patients in the study who had myocardial infarctions. In the other patients the difference in the rate of myocardial infarction between groups was not significant (0.2 percent in the rofecoxib group and 0.1 percent in the naproxen group). When the data showing a reduction in the rate of myocardial infarction in the naproxen group became available after the completion of this trial, Merck, the manufacturer of rofecoxib, notified all investigators in ongoing studies of a change in the exclusion criteria to allow patients to use low-dose aspirin. There was no association between hypertension and myocardial infarction; only a single patient (in the rofecoxib group) had both hypertension and a myocardial infarction as adverse events.

Figure 1. Time to Cardiovascular Adverse Event in the VIGOR Trial



No. at Risk							
Rofecoxib	4047	3643	3405	3177	2806	1067	531
Naproxen	4029	3647	3395	3172	2798	1073	514

Relative risk (95% confidence interval) = 2.38 (1.39-4.00); $P<.001$. VIGOR indicates Vioxx Gastrointestinal Outcomes Research.

Cardiovascular Thrombotic Events in Controlled, Clinical Trials of Rofecoxib

Marvin A. Konstam, MD; Matthew R. Weir, MD; Alise Reicin, MD; Deborah Shapiro, DrPh; Rhoda S. Sperling, MD; Eliav Barr, MD; Barry J. Gertz, MD, PhD

Background—In comparing aspirin, nonselective nonsteroidal antiinflammatory agents (NSAIDs), and cyclooxygenase (COX)-2 inhibitors, variation in platelet inhibitory effects exists that may be associated with differential risks of cardiovascular (CV) thrombotic events. Among the randomized, controlled trials with the COX-2 inhibitor rofecoxib, one study demonstrated a significant difference between rofecoxib and its NSAID comparator (naproxen) in the risk of CV thrombotic events. A combined analysis of individual patient data was undertaken to determine whether there was an excess of CV thrombotic events in patients treated with rofecoxib compared with those treated with placebo or nonselective NSAIDs.

Methods and Results—CV thrombotic events were assessed across 23 phase IIb to V rofecoxib studies. Comparisons were made between patients taking rofecoxib and those taking either placebo, naproxen (an NSAID with near-complete inhibition of platelet function throughout its dosing interval), or another nonselective NSAIDs used in the development program (diclofenac, ibuprofen, and nabumetone). The major outcome measure was the combined end point used by the Antiplatelet Trialists' Collaboration, which includes CV, hemorrhagic, and unknown deaths; nonfatal myocardial infarctions; and nonfatal strokes. More than 28 000 patients, representing >14 000 patient-years at risk, were analyzed. The relative risk for an end point was 0.84 (95% CI: 0.51, 1.38) when comparing rofecoxib with placebo; 0.79 (95% CI: 0.40, 1.55) when comparing rofecoxib with non-naproxen NSAIDs; and 1.69 (95% CI: 1.07, 2.69) when comparing rofecoxib with naproxen.

Conclusions—This analysis provides no evidence for an excess of CV events for rofecoxib relative to either placebo or the non-naproxen NSAIDs that were studied. Differences observed between rofecoxib and naproxen are likely the result of the antiplatelet effects of the latter agent. **(*Circulation*. 2001;104:2280-2288.)**

Key Words: rofecoxib ■ anti-inflammatory agents, nonsteroidal ■ cardiovascular diseases ■ thrombosis

Nonselective, nonsteroidal anti-inflammatory agents (NSAIDs), such as ibuprofen, diclofenac, nabumetone, naproxen, indomethacin, and aspirin inhibit both cyclooxygenase isoforms (COX-1 and COX-2) over their clinical dose range.[1] In contrast, rofecoxib is highly selective for only the COX-2 isoform over its clinical dose range.[2,3] In the gastrointestinal system, nonselective NSAIDs have been associated with gastroduodenal mucosal injury, whereas selective COX-2 inhibitors have demonstrated improved gastrointestinal safety and tolerability.[4–10] COX-1 inhibition has been associated with decreased synthesis of platelet-derived thromboxane, a vasoconstrictor and potent inducer of platelet aggregation.[11]

In comparing aspirin, nonselective NSAIDs, and COX-2 inhibitors, variation in platelet inhibitory effects may result in different influences on the rates of cardiovascular (CV) thrombotic events.[11] Sustained inhibition of COX-1–mediated thromboxane synthesis underlies the efficacy of aspirin in significantly reducing the incidence of CV death, myocardial infarction (MI), and stroke in high-risk patients.[11–14] Aspirin produces irreversible inhibition of platelet COX-1: this inhibition is near-complete and is sustained for at least 48 hours after a single dose.[14] In contrast to aspirin, nonselective NSAIDs are reversible inhibitors of COX-1: the extent and duration of inhibition closely follows their potency and systemic plasma drug concentrations, and the effect is reversible as a function of drug elimination.[14] Some evidence suggests that nonselective NSAIDs that mediate near-complete inhibition of platelet function throughout their entire dosing interval may be similar to aspirin and also

Received October 2, 2001; accepted October 3, 2001.

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Drs Konstam and Weir have been paid consultants to Merck and Co and Pharmacia, and Dr Konstam also has been a paid consultant to Pfizer Inc. Neither has been compensated for work on this article. Drs Reicin, Shapiro, Sperling, Barr, and Gertz are employees of Merck Research Laboratories, Merck and Co, Inc. As such, they receive financial compensation that includes stock ownership and stock options.

This article originally appeared Online on October 15, 2001 (*Circulation*. 2001;104:r15–r23).

Correspondence to Dr Marvin A. Konstam, New England Medical Center, Division of Cardiology, 750 Washington Street, Boston, MA 02111-1533. E-mail MKonstam@Lifespan.org

***Circulation* is available at http://www.circulationaha.org**

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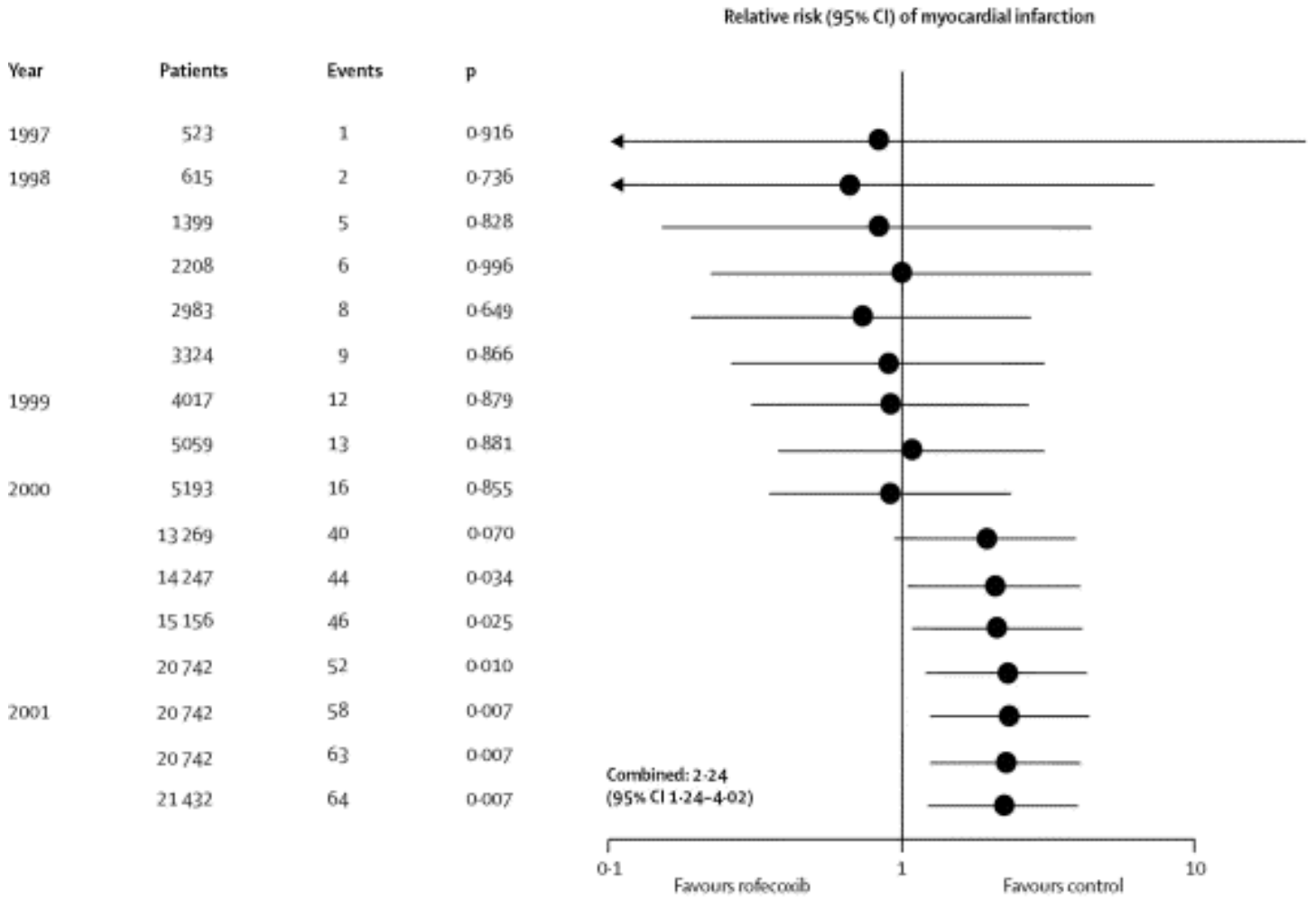
Risk of cardiovascular events: cumulative meta-analysis



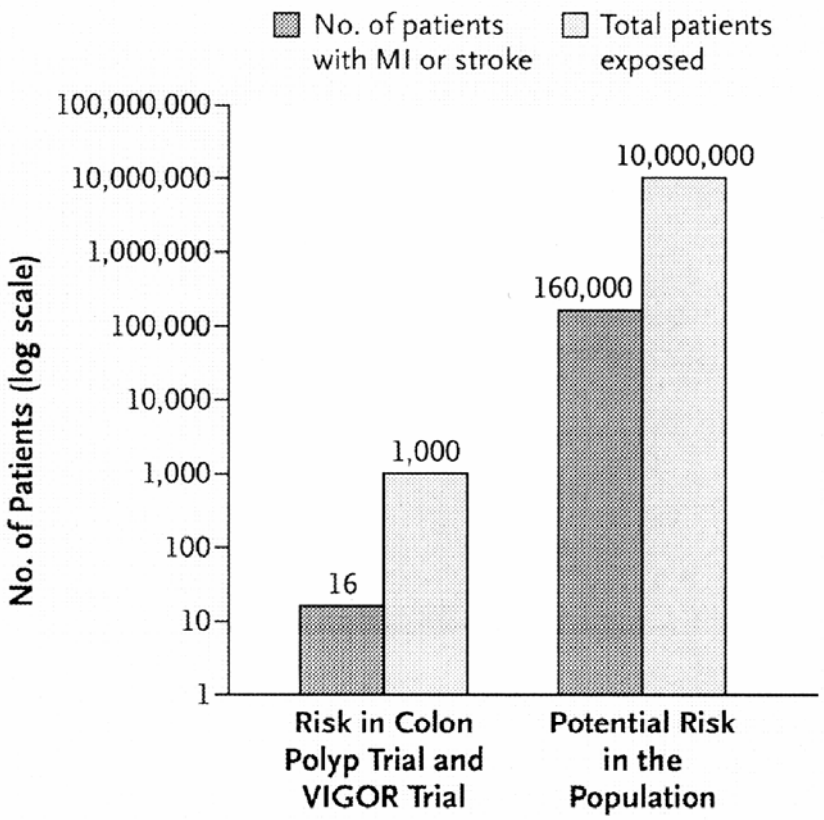
Juni et al. *Lancet*. 2004

Vioxx: 2001-4

- Several large epidemiologic studies suggest risk
- Annual sales: $1B
- Annual DTC advertising: >$100M

Vioxx: 2001-4

- Several large epidemiologic studies suggest risk
- Annual sales: $1B
- Annual DTC advertising: >$100M
- APPROVe study analysis:
  - 2600 patients (none with known CAD)
  - Incidence of MI/Stroke:
    - Vioxx – 3.5%
    - Placebo – 1.9%



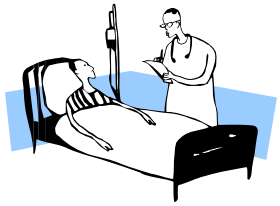
Risk of Myocardial Infarction (MI) or Stroke Associated with Rofecoxib Use.

Data are from Mukherjee et al.[2] and the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.

Bench to Bedside

Data Analysis
& Interpretation

Scientific Evidence

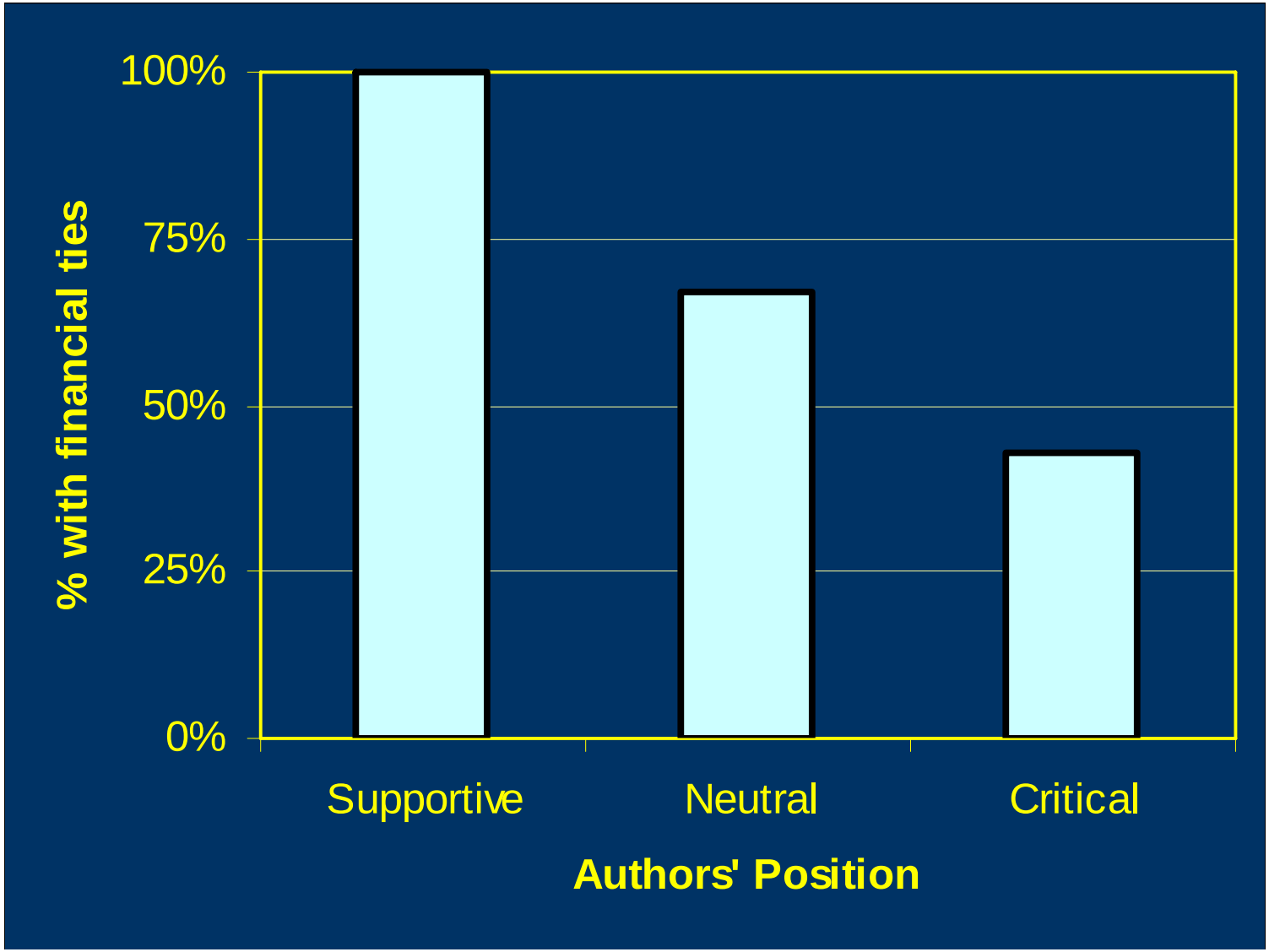


Conflicts of Interest and Interpretation

- 1995-1996 articles on the safety of Ca channel blockers.

- 70 articles
  - 5 original research papers
  - 32 reviews
  - 33 letter to the editor

Authors' published opinions were related to their financial arrangements



Bench to Bedside

Human Subjects

↓

Study Conduct

↓

Data Analysis & Interpretation

↓

Scientific Evidence

↓

journals - meetings - media

Jesse Gelsinger case

- Phase I gene therapy trial
- Treated-related death
- FDA investigation found:
  - lapses in notifying FDA re: 4 prior adverse reactions
  - Informed consent forms changed (omitting mention of animal deaths)
  - Gelsinger's ammonia was above acceptable level
- COI - U Penn, Dr. James Wilson (PI) both had equity in Genovo, Inc.

The Seattle Times

REPRINTED FROM MARCH 11-15, 2001

What patients at 'The Hutch' weren't told about the experiments in which they died

A five-part Seattle Times investigative series by Duff Wilson and David Heath

UNINFORMED CONSENT

Patients died prematurely in two failed clinical trials at Seattle's Fred Hutchinson Cancer Research Center — experiments using drugs in which the center and its doctors had a financial interest.

The patients and their families were never told about those connections, nor were they fully and properly informed about the risks of the experiments, an investigation by The Seattle Times has found.

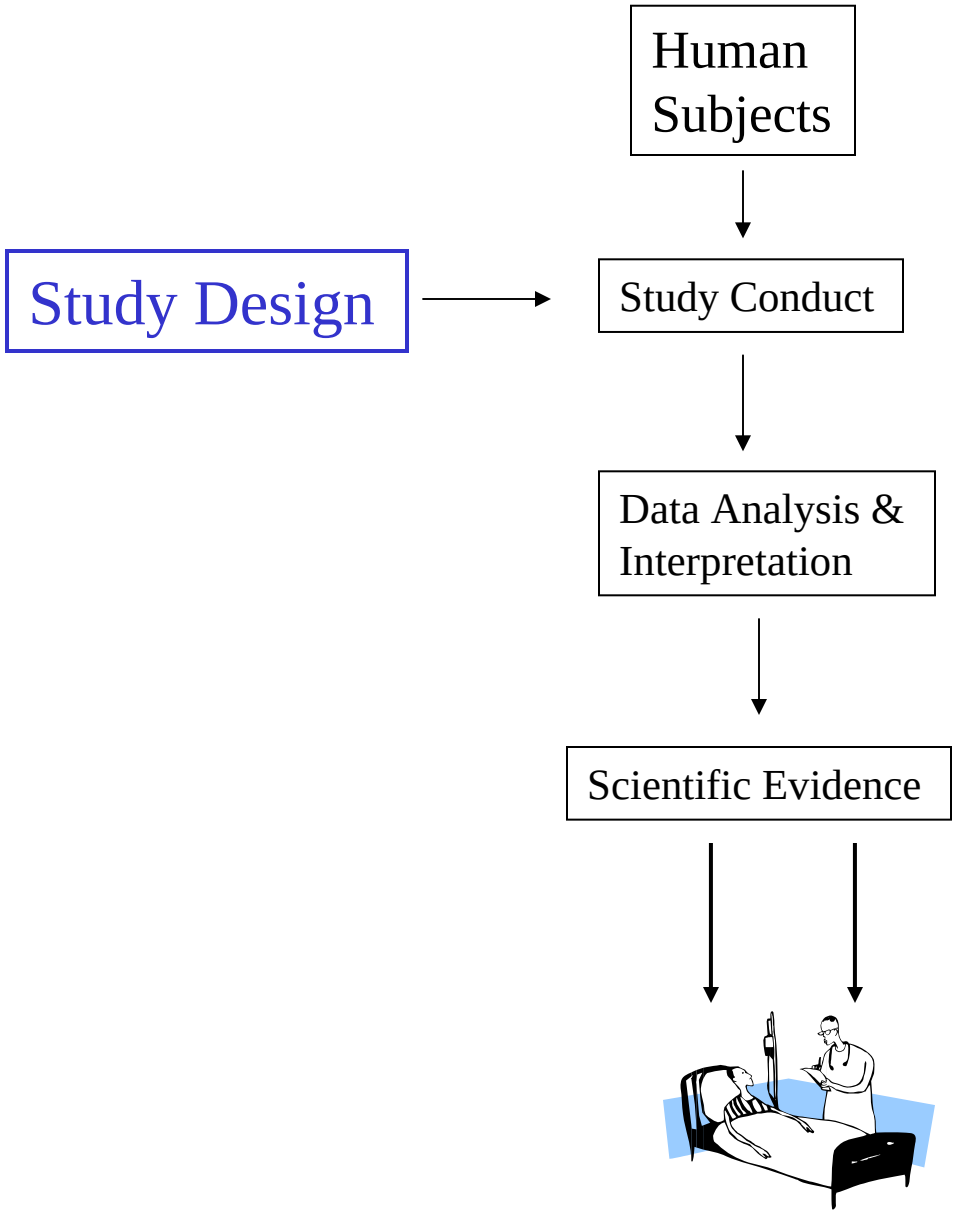
At any given time, about 100 clinical trials are under way at "The Hutch," one of the most respected cancer research centers in the world. Over the past year, The Times looked closely at two experiments testing drugs owned by companies in which Hutch doctors — including a Nobel Prize winner — held stock, advisory positions and, in some cases, jobs.

PART 1: THE BLOOD-CANCER EXPERIMENT

Both trials were sustained for long periods — a blood-cancer experiment from 1981 to 1993, a breast-cancer experiment from 1991 to 1998 — despite clear evidence they were failing.

In the blood-cancer trial, at least 20 patients died from causes attributable to the experiment. In the

Bench to Bedside

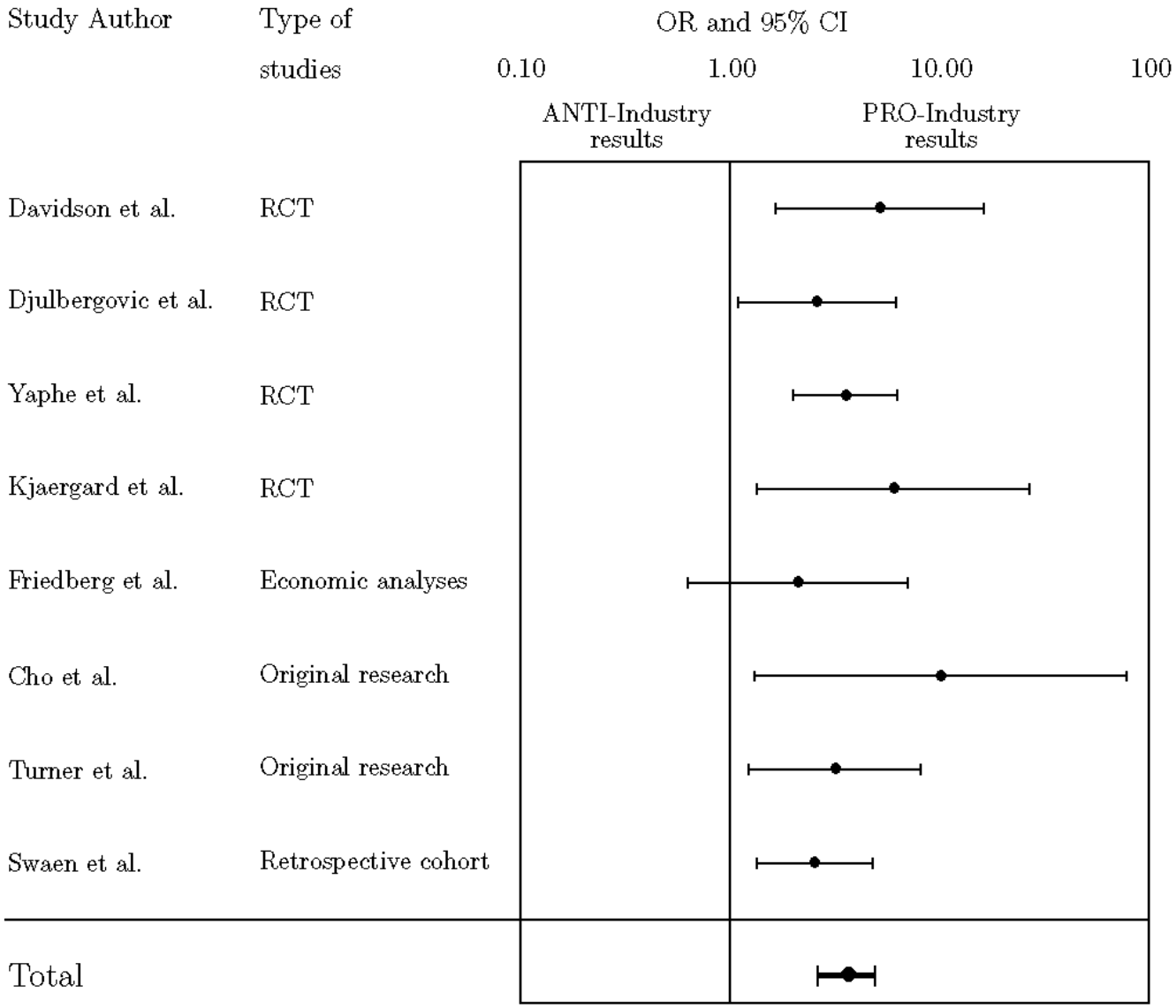


Study design bias

- Example: inferior comparison agents
- Fluconazole vs. amphotericin B
  - 92% of patients were in trials supported by the manufacturer of fluconazole.
  - *oral* amphotericin B used as comparison agent
    - poorly absorbed
    - rarely used for systemic infections
- Fluconazole looks like wonder-drug!

Johansen et al. JAMA. 282(18): 1752-1759

Systematic Review: Industry Sponsorship vs. Study Outcome



Bekelman et al. *JAMA*. 2003: 289: 454-65

Part II Summary: Financial Conflicts in Research are….

- Pervasive
- Powerful
- Clinically Hazardous
- A threat to scientific integrity

Part III: “Repairing” the Clinical Research System: Who is doing what?

- Societies
- Journals
- Government
- IRBs

ASCO restrictions for clinicians involved in research

- Finders fees
- Accrual bonuses
- Payment contingent upon research outcome
- Sponsor control of publication/dissemination of results.

ASCO – Restrictions on people in "leadership role"

- Stock/equity in trial sponsor
- Royalties/licensing fees
- Patents
- Position as officer/board member
- Honoraria

Journals

- Author Independence
- Publication Bias
- Objective Data Analysis

International Committee of Medical Journal Editors, 2001

"Editors may choose not to publish an article unless the authors":

- Have full access to study data
- Take responsibility for
  - Data integrity
  - Data analysis.
- Were free to publish results

Trial Registration

(required by ICMJE for trials starting after July, 2005)

- Hypothesis
- Interventions
- Endpoints
- Eligibility criteria
- Funding Source

ClinicalTrials.gov

JAMA Policy Regarding Data Analysis

Industry-sponsored studies in which the data analysis has been conducted only by statisticians employed by the sponsor:

- Independent statistician must be identified and given:
  - Entire raw data set
  - Study protocol and analytic plan
- Statistician must confirm analysis and findings, and report such in manuscript.

Fontanerosa et al. *JAMA*, 2005

Part III: “Repairing” the Clinical Research System: Who is doing what?

- Societies
- Journals
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Financial Conflicts at the NIH

- Prior to 2004, many NIH officials were permitted to keep consulting income confidential.
- Some high level officials, collected secondary income and stock options from biomedical companies.
- On December 7, 2003, the LA Times published an expose describing conflicts of interest among NIH employees. Some individuals reportedly collected $500K and more in consulting fees.

Willman, David. “Stealth Merger: Drug Companies and Government Medical Research.” NY Times 7 Dec. 2003.

"Conflict of Interest Information and Resources." 31 Aug. 2005. NIH. 20 Sept. 2005 <http://www.nih.gov/about/ethics_COI.htm>.

NIH Ban on Financial Conflicts

Feb, 2005

- Intramural Investigators
- Extremely Strict
  - What is Prohibited
    - Consulting
    - Speaking
    - Investments
  - Types of Entities
    - Industry
    - Hospitals
    - Insurers
    - Societies….

NIH Revised Ethics Regulations

- The top 200 NIH executives: biomedical stock holdings < $15,000.
- Roughly 6,000 other employees must submit their stock holdings for review for potential conflicts.
- NIH scientists permitted to:
  - hold fiduciary positions in medical societies
  - deliver medical education lectures paid for by drug companies.
  - Obtain outside employment involving interests unrelated to NIH duties

Gardiner, Harris. "*Health Agency Tightens Rules Governing Federal Scientists*." NY Times 26 Aug. 2005.

"Conflict of Interest Information and Resources." 31 Aug. 2005. NIH. 20 Sept. 2005 <http://www.nih.gov/about/ethics_COI.htm>.

Part III: “Repairing” the Clinical Research System: Who is doing what?

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Prospective Trial Participants are concerned about COI

	Heart Disease	**Breast Cancer**	**Depression**
Want to know financial arrangement	58%	69%	56%
Want researcher's information on informed consent form	68%	74%	64%
If researcher has financial interest, patient is less inclined to participate	22%	31%	28%

But what about actual study participants?

- Are they aware of COI as an issue?
- Are they worried about COI?
- Would COI's have affected their decision to enroll?

In the past six months, how much have you heard about financial ties related to clinical research studies in the news?

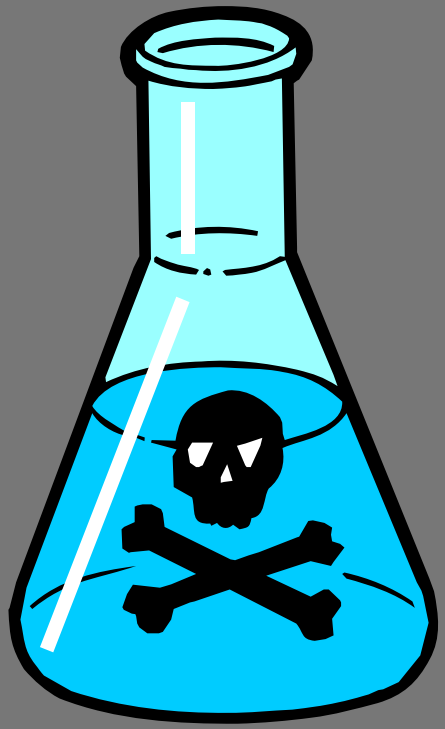
“A lot”	7%
“Moderate Amount”	16%
“Little/None”	77%

Sometimes *doctors* running clinical research studies have financial ties with the company that makes the drug used in the study. How worried, if at all, are you about your doctor at (cancer center) having these financial ties?

	RESEARCHER FINANCIAL TIES (Number=253)	CANCER CENTER FINANCIAL TIES (Number =253)
Very worried	1%	1%
Somewhat Worried	6%	7%
A Little Worried	11%	21%
Not Worried at All	80%	70%

Would COI have changed your decision?

	Stock	Consulting	Honoraria	Patent Royalty
No Effect on Participation	76%	75%	82%	70%
Stop Participation	11%	12%	9%	14%
Encourage Participation	1%	6%	4%	7%
Other*	11%	7%	6%	9%



Thank You!

		Researcher's Financial Ties
To Whom Should the Disclosure of Financial Ties be made	**Research Participants**	35%
	Cancer Center Administration	19%
	Independent Oversight Committee	32%
	Government Agency	3%
	Researcher or Cancer Center should decide who to tell	6%
	No one	2%
	Other	2%
What Should be Disclosed to Research Participants	**No Disclosure Required**	17%
	Disclosure if Financial Ties above a Monetary Threshold	9%
	Disclosure of All Financial Ties Regardless of Amount	31%
	Disclosure of Oversight System for Financial Ties	40%
	Other	2%